15 September
EMA/736888/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fycompa

perampanel

Procedure no: EMEA/H/C/002434/P46/024

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 06 June 2022, the MAH submitted a completed paediatric study for Fycompa oral suspension, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Perampanel is a highly selective non-competitive AMPA-type glutamate receptor antagonist. In the EU, Fycompa (perampanel), following the extension of indication in the paediatric population (EMEA/H/C/002434/II/0047), is indicated for the adjunctive treatment of:

- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.

- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

Perampanel has also been approved as monotherapy or adjunctive therapy in paediatric patients with POS aged 4 years and older in the US as of September 2018. The International Birth Date is 23 July 2012 in the EU (via the centralized procedure). Perampanel is marketed under the trade name Fycompa and is available as 2-, 4-, 6-, 8-, 10-, and 12-mg tablets and 0.5 mg/ml oral suspension.

EISAI is hereby submitting final study results and report related to paediatric population for Study E2007-G000-311 (referred to as Study 311). This study 311 is a required study in the perampanel Paediatric Investigation Plan (PIP), EMEA-000467-PIP01-08-M015, Study 9. Study 311 was a Phase 3, multicentre, open-label, single-arm study in children (aged 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTCS). The study enrolled 180 subjects (planned 160 subjects) and all subjects were treated with perampanel in the study. Of note, 146 subjects completed the Core Study, of which 136 subjects entered Extension A (refer to EMEA/H/C/002434/II/0047 extension of indication variation). And 53 subjects completed Extension A in Japan or France (those eligible to enrol in Extension B), of which 43 subjects entered Extension B.

The primary objective of the study was to evaluate the safety and tolerability of perampanel oral suspension as an adjunctive therapy in children (aged 4 to <12 years) with inadequately controlled POS or PGTCS.

The Core and Extension A data were already submitted and assessed in a Type II variation, procedure EMEA\H\C\002434\II\0047, to extend the approved indication for Fycompa to paediatric POS patients 4 to less than 12 years and PGTC of IGE patients 7 to less than 12 years that was approved on 10 Nov 2020. The Extension B data are now available and assessed in this submission.

The submission of these final data is being made to the European Medicines Agency to fulfil the obligation to present data from any MAH-sponsored study in a paediatric population.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Post-authorisation measure - Submission of paediatric study pursuant to article 46 of Regulation (EC) No 1901/2006 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product tested in Study 311 was Fycompa as 0.5 mg/ml oral suspension. Perampanel was orally administered once daily before bedtime.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study 311, multicentre, open-label, single-arm study in children (aged 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTCS to evaluate the safety and tolerability of perampanel oral suspension as an adjunctive therapy.

2.3.2. Clinical study

Description

The study was a Phase 3, multicenter, open-label, single-arm study in children (aged 4 to <12 years) with inadequately controlled POS or PGTCS. Subjects with complex partial seizures with secondary generalization, ie, secondarily generalized tonic-clonic seizures (SGTCS), were analyzed as a subset of the POS cohort. A total of 80 sites were selected, of which 58 sites enrolled subjects in Belgium (2), France (5), Hungary (4), Japan (22), Korea (1), Latvia (1), Poland (3), Spain (5), and the US (15). No adult subjects participated in this study.

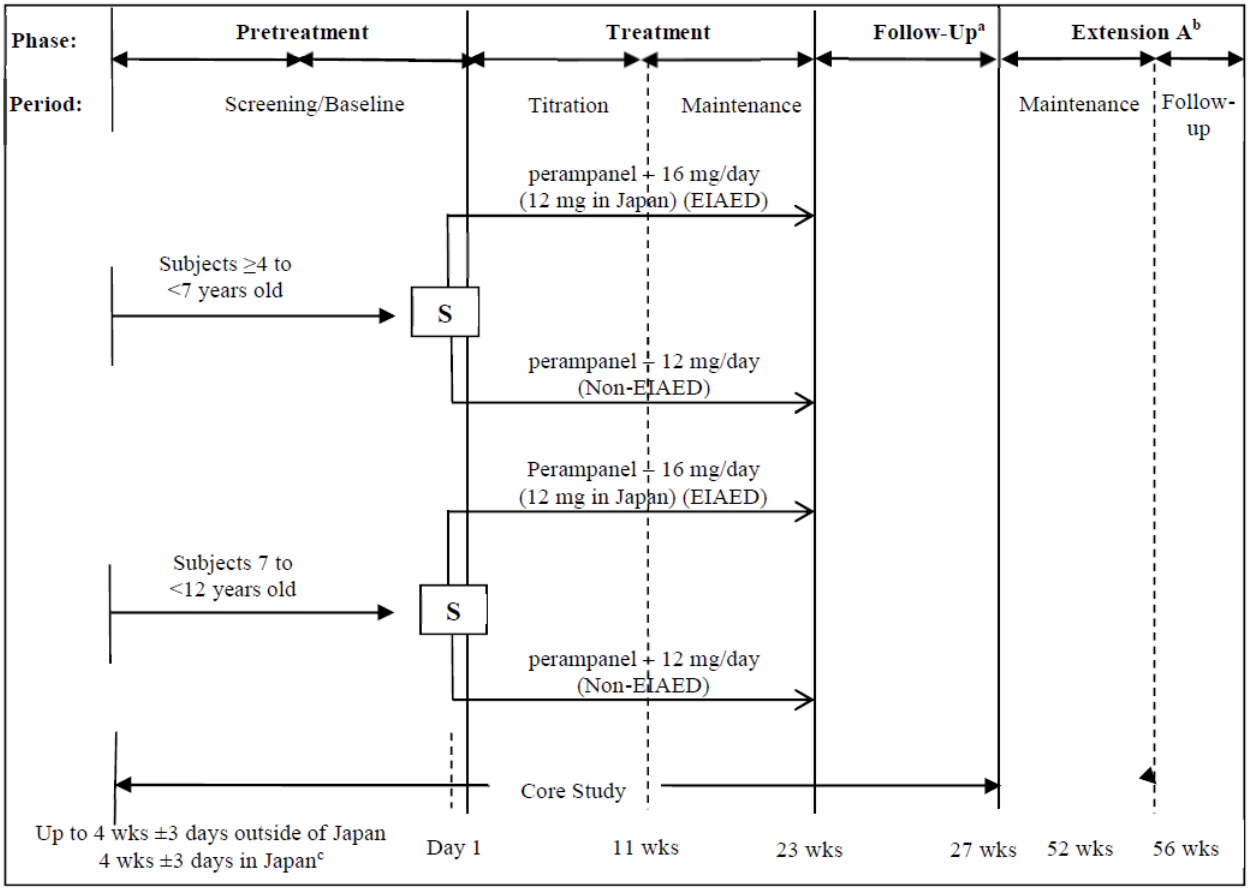
Subjects entered Extension B with their optimal perampanel dose (ie, the same dose of perampanel that they were maintained on at the end of Extension A). During the course of Extension B, doses of perampanel and concomitant antiepileptic drugs (AEDs) could be adjusted (concomitant AEDs could be used in accordance with the approved dosage and indication) based on clinical judgment. In Japan, the maximum dose of perampanel was 12 mg per day. In countries where an EAP could not be implemented, the maximum dose of perampanel was 12 mg per day in subjects not taking any concomitant enzyme-inducing antiepileptic drugs (EIAEDs), or 16 mg per day in subjects taking a concomitant EIAED.

Tolerability at a minimum perampanel dose of 2 mg per day was required to continue in the program. Subjects who did not tolerate the minimum perampanel dose of 2 mg per day during the study were to be discontinued from the study.

Conversion to monotherapy on perampanel was also permitted at the discretion of the investigator, if it was considered appropriate to control the seizures.

The visit intervals in Extension B were every 12 weeks. All visits were to be done within ±6 days of the schedule.

An overview of the study design (previous core study and extension A) is presented in Figure 1.



Note: Follow-up may have occurred during the Core Study (if the subject discontinued during the Core Study), or during Extension A or Extension B, after the termination of study treatment.
EIAED = enzyme-inducing antiepileptic drug, S = stratified, wks = weeks.

a: Subjects were to have a Follow-up Visit 4 weeks (±7 days) after the end of the treatment and a final assessment completed if they did not roll over into Extension A.

b: Subjects who were enrolled in Japan or in a country where an extended access program (EAP) was not implemented, and had completed the Extension A, were eligible to enroll in Extension B.

c: Subjects in Japan were required to complete 4 full weeks ±3 days of the Screening/Baseline Period.

CHMP comments:

The total study duration of study 311 from 1st subject enrolled to last subject's last visit/last assessment will be approximately 112 weeks (52 weeks of recruitment, up to 4 weeks ±3 days of Screening/Baseline, up to 52 weeks of treatment [including up to an 11-week Titration Period, up to 12-week Maintenance Period, and up to 29-week Extension Phase (Extension A)], and up to 4 weeks of follow-up [only for those subjects not entering into Extension B]). In Japan, 4 weeks ±3 days of baseline is required; however, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility has been established.

Extension Phase (Extension B) with open-label treatment will be available to subjects enrolled in Japan and in countries where an extended access program (EAP) cannot be implemented, after having completed Extension A. In Japan, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel is commercially available in Japan for treatment of partial-onset seizures (POS) inpediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available.

Overall the study 311 consisted of a Core Study and Extension A Phase for subjects globally as assessed during the EMEA/H/C/002434/II/0047 extension of indication variation, with an additional open-label Extension B available only for subjects enrolled in Japan and in countries where an extended access program (EAP) could not be implemented after completion of Extension A.

For more details regarding the methodology of study 311, refer to the assessment report of EMEA/H/C/002434/II/0047 extension of indication variation.

This variation focused on data collected from subjects who entered Extension B, up to time of the data cutoff (30 Mar 2020).

Methods

Study participants

To be eligible for Extension B, subjects must have resided in Japan or in countries where an EAP could not be implemented, must have completed the Core and Extension A of this study, were less than 12 years of age at the time of entering Extension B, and who, in the opinion of the investigator, would continue to benefit from treatment with perampanel.

During Extension B, the duration of treatment was to continue as long as clinically appropriate according to the judgment of the investigator. However, treatment was to be completed when a subject reached 12 years of age, switched to the commercial perampanel product, or discontinued for safety or administrative reasons.

Treatments

Fycompa as 0.5 mg/ml oral suspension were dosed orally once daily as per SmPC and standard clinical practice using commercially available oral suspension.

Objectives

The primary objective of the study was to evaluate the long-term safety and tolerability of perampanel oral suspension when administered as an adjunctive therapy in children (aged 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTCS).

There was no secondary objective for the Extension B of this study.

Outcomes /endpoints

For Extension B, only safety assessment.

Adverse events

AEs were coded using the MedDRA version 21.0 lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC were also captured in the database.

Only those AEs that occurred during Extension B for subjects in the Safety Analysis Set were included in summary tables.

The incidence of TEAEs were reported as the number (percentage) of subjects with TEAEs by SOC and PT.

The number (percentage) of subjects with TEAEs were also summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs were also summarized by relationship to study drug (Yes [possibly related, probably related] and No [not related]). AEs were analyzed by the actual dose at AE onset.

The number (percentage) of subjects with treatment-related TEAEs were summarized by SOC and PT. Treatment-related TEAEs included those events considered by the investigator to be related to study drug.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug, treatment-emergent serious adverse events (SAEs) and TEAEs leading to death were summarized by MedDRA SOC and PT.

Adverse Events of Special Interest

A listing of subjects with AEs related to suicidality, identified by the depression and suicide/self-injury Standardized MedDRA Query terms (SMQ), was provided. The TEAEs of special interest were summarized by SOC and PT. The SMQs were used to identify relevant terms for the following TEAEs:

• TEAEs suggestive of abuse potential: SMQ of drug abuse, dependence and withdrawal

• TEAEs related to alertness and cognition: SMQ of dementia

• TEAEs related to hostility/aggression: SMQ of hostility/aggression

• TEAEs related to psychosis/psychotic disorders: SMQ of psychosis and psychotic disorders

• TEAEs related to status epilepticus/convulsions: SMQ of convulsions

• TEAEs related to laboratory abnormalities: SMQ of drug-related hepatic disorders

• Cardiac and ECG TEAEs: SMQs of cardiac arrhythmia terms (including bradyarrhythmias and tachyarrythmias, arrhythmia related investigations, signs and symptoms, cardiac failure, cardiomyopathy, ischaemic heart disease, and Torsade de pointes/QT prolongation)

• TEAEs related to rash: TEAEs related to rash were identified by medical review

• Falls, regardless of causality, were summarized for the Extension B through Follow-up Period of the Extension phase, by the actual dose at onset.

Laboratory Values

Laboratory results were summarized using SI units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each post baseline visit and to the end of treatment (defined as the last on-treatment value) are summarized by visit using descriptive statistics. Qualitative parameters were summarized using frequencies (number and percentage of subjects), and changes from baseline to each post baseline visit and to end of treatment were reported using shift tables.

Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure, pulse, respiratory rate, temperature, weight) and changes from baseline were presented by visit. The number (percentage) of subjects with clinically notable results over all scheduled and unscheduled visits were summarized.

Sample size

There was no sample size calculation.

Randomisation and blinding (masking)

No randomization and blinding are anticipated for this study.

Statistical Methods

All safety analyses were performed on the Safety Analysis Set.

The Safety Analysis Set was defined as subjects who received at least 1 dose of perampanel and had at least 1 post-dose safety assessment in Extension B.

Safety data were summarized using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables).

Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and weight. Study Day 01 for all safety analyses was defined as the date of the first dose of study drug in the Core Study.

For completeness, subject data listings include cumulative data from Core Study through Extension A and Extension B for subjects who entered into Extension B.

Some data of 5 subjects captured in the electronic Case Report Forms (eCRFs) were not Source Data Verified (SDV) before database lock (Table 1). Due to the coronavirus disease 2019 (COVID-19) pandemic at the time, any non-urgent visits at study site were not allowed. These data did not have a significant impact on the overall study objectives and endpoints, and thus it was decided to proceed to database lock without SDV of the selected eCRF pages.

All summaries were generated by disease cohort (POS, SGTCS subset of POS, and PGTCS cohort), age cohort (4 to <7 years and ≥7 to <12 years), and inducer status (without concomitant EIAEDs and with concomitant EIAEDs). No summaries of subjects with IGE were produced since no subjects with IGE were enrolled in Extension B.

All analyses were conducted only for subjects who have participated in the Extension B, with baseline (before perampanel treatment initiation in Core Study) data being included where appropriate.

CHMP comments:

Taking into account the exceptional circumstances due to the coronavirus disease 2019 (COVID-19) pandemic at that time, the decision to lock the database without SDV of the selected eCRF pages of these 5 patients could be considered acceptable.

Results

Participant flow /recruitment

Reminder

- Core study:

Of the 208 subjects screened, 180 subjects were enrolled and treated in the Core Study (149 subjects in the POS cohort and 31 subjects in the PGTCS cohort). All 180 subjects were in the Safety Analysis Set (SAS) and in the Full Analysis Set (FAS).

Within the SAS, 46 subjects (POS: 40 and PGTCS: 6) were in the 4 to <7 year age group and 134 subjects (POS: 109 and PGTCS: 25) were in the ≥7 to <12 year age group.

Of the 180 subjects enrolled and treated in the Core Study, 146 (81.1%) subjects completed the Core Study (LSLV was 20 Jul 2018). The main reasons for discontinuation were adverse events (AEs) (14 [7.8%] subjects), subject choice (7 [3.9%] subjects), and inadequate therapeutic effect (8 [4.4%] subjects).

- Extension A phase:

Of the 146 subjects who completed the Core Study, 136 subjects entered Extension A (116 subjects in the POS cohort and 20 subjects in the PGTCS cohort).

Of the 136 subjects, 36 subjects (POS: 32 and PGTCS: 4) were in the 4 to <7 year age group and 100 subjects (POS: 84 and PGTCS: 16) were in the ≥7 to <12 year age group.

A total of 122 (89.7%) subjects completed Extension A (LSLV was 05 Feb 2019). The main reasons for discontinuation of perampanel treatment in Extension A were AEs (5 [3.7%] subjects), inadequate therapeutic effect (4 [2.9%] subjects) and subject choice (3 [2.2%] subjects).

Patient disposition for Extension B:

Of the 53 (100.0%) subjects who completed Extension A in Japan or France, 43 subjects (81.1%) (41 subjects in Japan and 2 subjects in France) entered Extension B (42 subjects in the POS cohort and 1 subject in the PGTCS cohort). Of the 42 treated subjects, 11 subjects (all in the POS cohort) were in the 4 to <7 year age group and 31 subjects (POS: 30 and PGTCS: 1) were in the ≥7 to <12 year age group.

See table 2 for subject disposition in the Extension B of study 311:

Table 2 Subject Disposition and Primary Reason for Discontinuation from Study by Disease Cohort – All Enrolled Subjects – Extension B

	Disease Cohort			
	POS (N=42)	PGTCS (N=1)	SGTCS (N=22)	Total (N=43)
Enrolled in Extension B, n	42	1	22	43
Not treated, n	1	0	0	1
Treated, n (%)	41 (100.0)	1 (100.0)	22 (100.0)	42 (100.0)
Completed Extension B, n (%)	35 (85.4)	1 (100.0)	18 (81.8)	36 (85.7)
Discontinued Extension B, n (%)	5 (12.2)	0	4 (18.2)	5 (11.9)
Ongoing in Extension Phase B, n (%)	1 (2.4)	0	0	1 (2.4)
Primary reason for discontinuation from Extension B[a], n (%)				
Adverse event[b]	0	0	0	0
Subject choice	1 (2.4)	0	1 (4.5)	1 (2.4)
Inadequate therapeutic effect	3 (7.3)	0	2 (9.1)	3 (7.1)
Other	1 (2.4)	0	1 (4.5)	1 (2.4)

CHMP comments:

A total of 122 (89.7%) subjects completed Extension A phase considering all concerned countries: Belgium, France, Hungary, Japan, Korea, Latvia, Poland, Spain and the US.

The Extension B involves subjects who completed Extension A phase only in Japan or France (53 subjects) and therefore implies a reduced proportion of those who overall completed Extension A phase.

Of the 42 treated subjects, 36 (85.7%) subjects completed Extension B as of data cut-off date of 30 Mar 2020. Five (11.9%) subjects were withdrawn early from Extension B. The main reasons for discontinuation of perampanel treatment in Extension B were inadequate therapeutic effect (3 [7.1%] subjects), subject choice (1 [2.4%] subject) and other reasons (1 [2.4%] subject).

One subject in [redacted] (Subject [redacted]; POS cohort, 4 to <7 years old without-concomitant-EIAEDs cohort) was ongoing in the study at the time of data cut-off. This last subject completed the study on 06 Dec 2021.

One subject was [redacted] just when [redacted] completed Extension A and entered Extension B, and thus was switched to commercial Fycompa and did not receive study drug in Extension B.

Baseline data

The main demographic and baseline characteristics by disease cohort during the Extension B are displayed in Table 3.

Table 3 Demographic and Baseline Characteristics by Disease Cohort - Safety Analysis Set - Extension B

Category	Disease Cohort			Total (N=42)
	POS (N=41)	PGTCS (N=1)	SGTCS (N=22)	
Age (years)[a]				
Mean (SD)	7.8 (1.81)	9.0 (NA)	7.8 (1.79)	7.8 (1.80)
Median (min, max)	8.0 (4, 10)	9.0 (9, 9)	8.0 (5, 10)	8.0 (4, 10)
Age group, n (%)				
4 to <7 years	11 (26.8)	0	6 (27.3)	11 (26.2)
≥7 to <12 years	30 (73.2)	1 (100.0)	16 (72.7)	31 (73.8)
Sex, n (%)				
Male	19 (46.3)	1 (100.0)	7 (31.8)	20 (47.6)
Female	22 (53.7)	0	15 (68.2)	22 (52.4)
Race, n (%)				
White	0	0	0	0
Black or African American	0	0	0	0
Japanese	40 (100.0)	0	22 (100.0)	40 (100.0)
Other Asian	0	0	0	0
American Indian or Alaska Native	0	0	0	0
Other	0	0	0	0
Missing	1	1	0	2
Weight (kg)				
Mean (SD)	22.53 (6.316)	28.80 (NA)	22.55 (6.699)	22.68 (6.313)
Median (min, max)	20.20 (16.1, 44.8)	28.80 (28.8, 28.8)	20.10 (16.1, 44.8)	20.70 (16.1, 44.8)
BMI (kg/m^2)				
Mean (SD)	15.12 (2.412)	15.46 (NA)	15.30 (2.522)	15.13 (2.383)
Median (min, max)	14.42 (11.6, 22.8)	15.46 (15.5, 15.5)	14.33 (12.0, 22.8)	14.51 (11.6, 22.8)
Time since diagnosis (years)[b]				
Mean (SD)	6.305 (2.6626)	8.758 (NA)	6.234 (2.6624)	6.364 (2.6570)
Median (min, max)	6.125 (0.53, 10.42)	8.758 (8.76, 8.76)	5.854 (0.53, 10.39)	6.355 (0.53, 10.42)

CHMP comments:

Of the 42 treated subjects in Extension B, there were 22 (52.4%) female subjects and 20 (47.6%) male subjects. The majority of the subjects was Japanese (40 subjects). The mean (SD) values of age, weight, and body mass index (BMI) were 7.8 (1.80) years, 22.68 (6.313) kg, and 15.13 (2.383) kg/m2, respectively. The median time since diagnosis was 6.355 years.

Regarding the concomitant AED, a protocol amendment had changed the inclusion/exclusion criteria to increase the maximum number of approved AEDs from 2 to 3 to improve subjects' enrolment.

Extent of exposure

In Extension B Safety Analysis Set (N=42), across the disease cohorts, the median (range) duration of exposure was 63.0 (9 to 89) weeks and the mean (SD) duration of exposure was 55.9 (24.38) weeks.

The mean (SD) of mean daily dose of perampanel was 7.8 (2.70) mg/day. The mean (SD) of mean daily dose of perampanel by disease cohorts were: POS – 7.8 (2.74) mg/day, SGTCS – 7.5 (3.27) mg/day, and PGTCS – 8.0 (NA) mg/day and by age cohorts: 4 to <7 years - 6.7 (2.78) mg/day and ≥7 to <12 years - 8.2 (2.62) mg/day. When analyzed across the concomitant EIAEDs cohorts, the mean perampanel dose appeared to be similar in subjects in the with-concomitant-EIAEDs cohort (mean [SD] daily dose 7.6 [3.19] mg/day; maximum dose received 9.0 [3.46] mg/day), relative to those in the without-concomitant-EIAEDs cohort (mean daily dose 7.8 [2.70] mg/day; maximum dose received 8.4 [2.90] mg/day).

CHMP comments:

The majority (≥70%) of subjects who entered Extension B had cumulative exposure to perampanel for more than 100 weeks: 29 [70.7%] subjects in the POS cohort, 15 [68.2%] subjects in SGTCS cohort, and 1 [100.0%] subject in the PGTCS cohort from study drug treatment initiation through end of treatment in Extension B.

The overall median duration of exposure was 116.7 weeks (range: 59 – 141 weeks), which was similar across disease cohorts (POS: 116.1 weeks, SGTCS: 114.0 weeks, and PGTCS: 120.6 weeks), between the two age cohorts (4 to <7 years: 124.0 weeks and ≥7 to <12 years: 116.0 weeks), and between subjects with or without concomitant EIAEDs (123.9 weeks and 116.1 weeks, respectively).

Overall, based on the cumulative data throughout the Core Study, Extension A, and Extension B, the average (SD) of the mean daily dose of perampanel was 7.5 (2.27) mg/day, which was similar across disease cohorts (POS: 7.4 [2.30] mg/day, SGTCS: 7.4 [2.78] mg/day, and PGTCS: 7.9 [NA] mg/day), between the two age cohorts (4 to <7 years: 7.1 [2.01] mg/day, ≥7 to <12 years: 7.6 [2.37] mg/day), and between subjects with or without concomitant EIAEDs (7.5 [1.66] mg/day and 7.5 [2.34] mg/day, respectively).

Efficacy results

No efficacy evaluations were performed during Extension B.

CHMP comments:

In study 311, efficacy was a secondary objective as measured by the median percent change in seizure frequency per 28 days, responder rates (≥25%, ≥50%, ≥75%) and seizure-free rate, and CGIC.

For the Core Study, efficacy analyses were performed using the FAS (N=180 subjects) including data from baseline through end of treatment during the Core Study (up to 23 weeks of treatment).

For the Core and Extension A, efficacy analyses were performed using the Core FAS (N=180 subjects) including data from baseline through end of treatment during the Core Study or Extension A (up to 52 weeks of treatment).

See EMEA/H/C/002434/II/0047 clinical assessment report for more details.

Safety results

Core study and extension A

CHMP comments:

For safety results during core study and extension A, see EMEA/H/C/002434/II/0047 clinical assessment report for more details.

Reminder: in the conclusion, the MAH was requested to continue to monitor the puberty / sexual maturation and skeletal development in the ongoing paediatric study (Studies 236) and in the future PSUR. The extension B of study 311 is not designed to provide these data.

Extension B

- **Overview of Adverse Events**

The AEs are presented Table 4 below for subjects in the Extension B Safety Analysis Set:

Table 4 Overview of Treatment-Emergent Adverse Events in Extension B by Disease Cohort – Safety Analysis Set - Extension B

Category	Disease Cohort			Total (N=42) n (%)
	POS (N=41) n (%)	PGTCS (N=1) n (%)	SGTCS (N=22) n (%)	
TEAEs	34 (82.9)	1 (100.0)	17 (77.3)	35 (83.3)
Treatment-related TEAEs	5 (12.2)	1 (100.0)	3 (13.6)	6 (14.3)
Severe TEAEs	6 (14.6)	0	2 (9.1)	6 (14.3)
Serious TEAEs	8 (19.5)	0	4 (18.2)	8 (19.0)
Deaths	0	0	0	0
Other SAEs	8 (19.5)	0	4 (18.2)	8 (19.0)
Life threatening	0	0	0	0
Requires inpatient hospitalization or prolongation of existing hospitalization	8 (19.5)	0	4 (18.2)	8 (19.0)
Persistent or significant disability or incapacity	0	0	0	0
Congenital anomaly/birth defect	0	0	0	0
Important medical events	0	0	0	0
TEAEs leading to study drug dose adjustment	2 (4.9)	0	2 (9.1)	2 (4.8)
TEAEs leading to study drug withdrawal	0	0	0	0
TEAEs leading to study drug dose increase	0	0	0	0
TEAEs leading to study drug dose reduction	2 (4.9)	0	2 (9.1)	2 (4.8)
TEAEs leading to study drug dose interruption	0	0	0	0

Overall in Extension B, 35 (83.3%) subjects experienced TEAEs: 34 (82.9%) subjects in the POS cohort, including 17 (77.3%) subjects in the SGTCS subset of the POS cohort, and 1 (100.0%) subject in the PGTCS cohort. TEAEs were reported for 10 (90.9%) subjects in the 4 to <7 years cohort and 25 (80.6%) subjects in the ≥7 to <12 years cohort; and for 3 (75.0%) subjects in the with-concomitant-EIAEDs cohort and 32 (84.2%) subjects in the without-concomitant-EIAEDs cohort.

- Treatment-Emergent Adverse Events by Severity

The majority of subjects experienced TEAEs that were either mild (14 [33.3%] subjects) or moderate (15 [35.7%] subjects) in severity. Overall, 6 (14.3%) subjects had severe TEAEs: 6 (14.6%) subjects in the POS cohort, including 2 (9.1%) subjects in the SGTCS subset of the POS cohort. No severe TEAEs were reported in the PGTCS cohort. Of the 6 subjects with severe TEAEs, 1 (9.1%) subject was in the 4 to <7 years age cohort and 5 (16.1%) subjects were in ≥7 to <12 years age cohort.

CHMP comments:

Most severe TEAE were related to infections and infestations or respiratory, thoracic and mediastinal disorders MedDRA SOC.

- Treatment-related TEAEs

The majority of TEAEs reported were deemed not related to perampanel. Treatment-related TEAEs were reported for 6 (14.3%) subjects overall: 5 (12.2%) subjects in the POS cohort, including 3 (13.6%) subjects in the SGTCS subset of the POS cohort, and 1 (100.0%) subject in the PGTCS cohort. Of the 6 subjects with treatment-related TEAEs, 1 (9.1%) subject was in the 4 to <7 years age cohort and 5 (16.1%) subjects were in ≥7 to <12 years age cohort.

Table 14.3.1.5.2
Treatment-Related, Treatment-Emergent Adverse Events in Extension Phase B by System Organ Class and Preferred Term by Age Cohort
Safety Analysis Set - Extension Phase B

MedDRA System Organ Class Preferred Term	Age Cohort 4 to <7 years (N=11) n (%)	 7 to <12 years (N=31) n (%)	 Total (N=42) n (%)
Subjects with any TEAE	1 (9.1)	5 (16.1)	6 (14.3)
Gastrointestinal disorders	0	1 (3.2)	1 (2.4)
Dysphagia	0	1 (3.2)	1 (2.4)
Hepatobiliary disorders	0	1 (3.2)	1 (2.4)
Drug-induced liver injury	0	1 (3.2)	1 (2.4)
Investigations	0	1 (3.2)	1 (2.4)
Gamma-glutamyltransferase increased	0	1 (3.2)	1 (2.4)
Nervous system disorders	0	1 (3.2)	1 (2.4)
Headache	0	1 (3.2)	1 (2.4)
Somnolence	0	1 (3.2)	1 (2.4)
Skin and subcutaneous tissue disorders	1 (9.1)	1 (3.2)	2 (4.8)
Nail dystrophy	0	1 (3.2)	1 (2.4)
Yellow skin	1 (9.1)	0	1 (2.4)

CHMP comments:

The treatment-related TEAEs included 1 yellow skin in a subject of the 4 to <7 years age cohort and 1 dysphagia, 1 DILI, 1 GGT increased, 1 headache and 1 somnolence in one subject each of the ≥7 to <12 years age cohort.

- Death and other major issues

No TEAEs leading to death, life-threatening situations, persistent or significant disability or incapacity or important medical events were reported during the study.

- SAE

A total of 8 (19.0%) subjects (8 [19.5%] subjects in the POS cohort, including 4 [18.2%] subjects in the SGTCS subset of the POS cohort) experienced treatment-emergent SAEs. Treatment-emergent SAEs were not reported for the subject in the PGTCS cohort. None of the SAEs reported during Extension B were assessed by the investigator as related to study drug.

Table 14.3.2.2.1
Treatment-Emergent Serious Adverse Events in Extension Phase B by System Organ Class and Preferred Term by Disease Cohort
Safety Analysis Set - Extension Phase B

MedDRA System Organ Class Preferred Term	Disease Cohort POS (N=41) n (%)	PGTC (N=1) n (%)	SGTC (N=22) n (%)	Total (N=42) n (%)
Subjects with any TESAE	8 (19.5)	0	4 (18.2)	8 (19.0)
Gastrointestinal disorders	1 (2.4)	0	0	1 (2.4)
Enterocolitis	1 (2.4)	0	0	1 (2.4)
Infections and infestations	6 (14.6)	0	3 (13.6)	6 (14.3)
Bronchitis	1 (2.4)	0	1 (4.5)	1 (2.4)
Lower respiratory tract infection	1 (2.4)	0	1 (4.5)	1 (2.4)
Pharyngitis	1 (2.4)	0	0	1 (2.4)
Pneumonia	5 (12.2)	0	2 (9.1)	5 (11.9)
Pyelonephritis acute	1 (2.4)	0	0	1 (2.4)
Respiratory, thoracic and mediastinal disorders	2 (4.9)	0	0	2 (4.8)
Pneumonia aspiration	1 (2.4)	0	0	1 (2.4)
Upper respiratory tract inflammation	1 (2.4)	0	0	1 (2.4)
Vascular disorders	1 (2.4)	0	1 (4.5)	1 (2.4)
Subgaleal haematoma	1 (2.4)	0	1 (4.5)	1 (2.4)

CHMP comments:

None of the 8 SAEs (enterocolitis, bronchitis, lower respiratory tract infection, pharyngitis, pneumonia, pyelonephritis acute, pneumonia aspiration, upper respiratory tract inflammation, subgaleal haematoma) reported during Extension B was assessed by the investigator as related to study drug. All occurred in the POS cohort and none in the PGTCS cohort.

- TEAEs Leading to Discontinuation

No subject in Extension B discontinued the study drug due to a TEAE.

- TEAEs Requiring Interruption, Dose Reduction of Perampanel or withdrawal

Overall, TEAEs leading to dose reduction were reported by 2 (4.8%) subjects (both in the SGTCS subset of the POS cohort). Both subjects were in the ≥7 to <12 years and without-concomitant-EIAEDs cohorts. There were no subjects with TEAEs that led to dose interruption, dose increase or withdrawal.

- **Common Treatment-Emergent Adverse Events**

Common TEAEs (in at least 10% of subjects in any disease cohort) are summarized by MedDRA (Version 21.0) SOC and PT in Table 5 below:

Table 5 Treatment-Emergent Adverse Events in Extension B by Disease Cohort Experienced by More than One Subject by System Organ Class and Preferred Term – Safety Analysis Set - Extension B

MedDRA System Organ Class Preferred Term	Disease Cohort POS (N=41) n (%)	PGTCS (N=1) n (%)	SGTCS (N=22) n (%)	Total (N=42) n (%)
Subjects with any TEAE	34 (82.9)	1 (100.0)	17 (77.3)	35 (83.3)
Eye disorders	9 (22.0)	0	7 (31.8)	9 (21.4)
Conjunctivitis allergic	4 (9.8)	0	3 (13.6)	4 (9.5)
Keratitis	2 (4.9)	0	2 (9.1)	2 (4.8)
Gastrointestinal disorders	16 (39.0)	0	9 (40.9)	16 (38.1)

Constipation	2 (4.9)	0	2 (9.1)	2 (4.8)
Dental caries	2 (4.9)	0	1 (4.5)	2 (4.8)
Diarrhoea	3 (7.3)	0	2 (9.1)	3 (7.1)
Vomiting	5 (12.2)	0	3 (13.6)	5 (11.9)
General disorders and administration site conditions	4 (9.8)	0	3 (13.6)	4 (9.5)
Pyrexia	4 (9.8)	0	3 (13.6)	4 (9.5)
Infections and infestations	30 (73.2)	1 (100.0)	14 (63.6)	31 (73.8)
Bronchitis	4 (9.8)	0	3 (13.6)	4 (9.5)
Conjunctivitis	4 (9.8)	0	2 (9.1)	4 (9.5)
Gastroenteritis	1 (2.4)	1 (100.0)	0	2 (4.8)
Influenza	6 (14.6)	0	3 (13.6)	6 (14.3)
Lower respiratory tract infection	2 (4.9)	0	1 (4.5)	2 (4.8)
Nasopharyngitis	14 (34.1)	0	8 (36.4)	14 (33.3)
Pharyngitis	2 (4.9)	0	1 (4.5)	2 (4.8)
Pneumonia	5 (12.2)	0	2 (9.1)	5 (11.9)
Streptococcal infection	3 (7.3)	0	1 (4.5)	3 (7.1)
Upper respiratory tract infection	3 (7.3)	0	1 (4.5)	3 (7.1)
Varicella	2 (4.9)	0	1 (4.5)	2 (4.8)
Investigations	5 (12.2)	0	2 (9.1)	5 (11.9)
Gamma-glutamyltransferase increased	2 (4.9)	0	1 (4.5)	2 (4.8)
Psychiatric disorders	5 (12.2)	0	4 (18.2)	5 (11.9)
Insomnia	2 (4.9)	0	2 (9.1)	2 (4.8)
Respiratory, thoracic and mediastinal disorders	8 (19.5)	0	4 (18.2)	8 (19.0)
Upper respiratory tract inflammation	3 (7.3)	0	2 (9.1)	3 (7.1)
Skin and subcutaneous tissue disorders	11 (26.8)	1 (100.0)	5 (22.7)	12 (28.6)
Dermatitis	3 (7.3)	0	2 (9.1)	3 (7.1)
Eczema	2 (4.9)	0	0	2 (4.8)
Rash	2 (4.9)	0	1 (4.5)	2 (4.8)

Common TEAEs overall and by disease cohorts were as follows:

- Overall (N=42): nasopharyngitis (14 [33.3%] subjects), influenza (6 [14.3%] subjects), and pneumonia and vomiting (5 [11.9%] subjects each)
- In the POS cohort (N=41): nasopharyngitis (14 [34.1%] subjects), influenza (6 [14.6%] subjects), and vomiting and pneumonia (5 [12.2%] subjects each)
- In the SGTCS subset of the POS cohort (N=22): nasopharyngitis (8 [36.4%] subjects) and conjunctivitis allergic, vomiting, pyrexia, bronchitis, and influenza (3 [13.6%] subjects each)
- In the PGTCS cohort (N=1): gastroenteritis and nail dystrophy (1 [100.0%] subject each).

The most common TEAEs reported in at least 10% of subjects by age cohorts were as follows:

- 4 to <7 years cohort: nasopharyngitis (4 [36.4%] subjects), pyrexia, influenza, and upper respiratory tract inflammation (3 [27.3%] subjects each), conjunctivitis allergic, vomiting, conjunctivitis, Streptococcal infection, dermatitis, and eczema (2 [18.2%] subjects each).
- ≥7 to <12 years cohort: nasopharyngitis (10 [32.3%] subjects) and pneumonia (4 [12.9%] subjects).

CHMP comments:

Most frequently reported TEAEs that occurred in more than 10% of subjects overall were nasopharyngitis, influenza, pneumonia, and vomiting. None of these TEAE observed in at least 10% of subjects in any disease cohort are stated in the SmPC of Fycompa and are considered treatment related.

- **Analysis of Adverse Events**

– Treatment-Emergent Adverse Events Suggestive of *Abuse Potential*

No TEAEs related to abuse potential were identified.

– Treatment-Emergent Adverse Events Related to *Alertness or Cognition*

In the search for narrow and broad SMQ terms, TEAEs related to alertness and cognition were reported by 2 (4.8%) subjects, of which both were in the SGTCS subset of the POS cohort, in the ≥7 to <12 years, and without-concomitant-EIAEDs cohorts. These TEAEs included restlessness and somnolence in 1 subject each.

CHMP comments:

The TEAE restlessness is not stated in the SmPC of Fycompa and is not considered related to the treatment by the investigator.

– Treatment-Emergent Adverse Events Related to *Hostility/Aggression*

1 TEAE related to hostility/aggression of irritability was reported by 1 (2.4%) subject in the POS cohort, in the ≥7 to <12 years, and with-concomitant-EIAEDs cohorts.

CHMP comments:

The TEAE irritability is already stated in the SmPC of Fycompa and more frequently observed in the paediatric population.

– Treatment-Emergent Adverse Events Related to *Psychosis/Psychotic Disorders*

No TEAEs related to Psychosis/Psychotic Disorders were reported by subjects in Extension B.

– Treatment-Emergent Adverse Events Related to *Status Epilepticus/Convulsions*

One TEAE of seizure cluster was reported by 1 (2.4%) subject (POS, ≥7 to <12 years, and without-concomitant-EIAEDs cohorts.

CHMP comments:

The TEAE seizure cluster is not stated in the SmPC of Fycompa and is not considered related to the treatment by the investigator.

– Treatment-Emergent Adverse Events Related to *Laboratory Abnormalities*

Overall, TEAEs of drug-related hepatic disorders were reported in 4 (9.5%) subjects with 4 (9.8%) subjects in the POS cohort, including 1 (4.5%) subject in the SGTCS subset of the POS cohort, and 2 subjects in each of the age cohorts. The events reported included gamma-glutamyl transferase (GGT) increased (2 [4.8%] subjects), alanine aminotransferase (ALT) increased, ammonia increased, aspartate aminotransferase (AST) increased, drug-induced liver injury, and yellow skin (1 [2.4%] subject each). All subjects were from the without-concomitant-EIAEDs cohort, except for the subject with drug-induced liver injury (≥7 to <12 years cohort). These changes did not meet Hy's Law criteria.

CHMP comments:

The TEAE related to hepatic laboratory abnormalities is already stated in the SmPC of Fycompa as a special warning and precaution for use. The increased gamma-glutamyl transferase (GGT), the drug-induced liver injury and the yellow skin are considered related to the treatment by the investigator. The drug-induced liver injury occurred in the concomitant-EIAEDs cohort which could partly mitigate its relation.

- *Cardiac and ECG* TEAEs

No cardiac or ECG TEAEs were reported by subjects in Extension B.

- *Pregnancy*

No positive pregnancy results were reported for subjects in Extension B.

- TEAEs Related to *Rash*

Overall, TEAEs related to rash were reported by 14 (33.3%) subjects, of which 14 (34.1%) subjects were in the POS cohort, including 6 (27.3%) subjects in the SGTCS subset of the POS cohort. The TEAEs related to rash were reported for 5 (45%) subjects in the 4 to <7 years cohort and for 9 (29.0%) subjects in the ≥7 to <12 years cohort. Thirteen (34.2%) subjects in the without-concomitant-EIAEDs cohort and 1 (25.0%) subject in the with-concomitant-EIAEDs cohort had TEAEs related to rash.

The TEAEs related to rash that occurred in more than 1 subject included events of dermatitis (3 [7.1%] subjects), and eczema, rash, and varicella (2 [4.8%] subjects each).

CHMP comments:

According to the SmPC, severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS)and Stevens - Johnson Syndrome (SJS), which can be life-threatening or fatal, have been reported with Fycompa. No such severe cutaneous AE have been observed. Fourteen rashes were observed and none was considered related to treatment by the investigator. The only cutaneous TEAE considered related to treatment by the investigator were nail dystrophia and yellow skin (see laboratory abnormalities above).

- TEAEs Related to *Suicidality*

Subject [redacted] ([redacted], [redacted], [redacted]) in the SGTCS subset of the POS cohort, taking a 4 mg dose of perampanel, reported a non-serious, TEAE of intentional self-injury, which were assessed by the investigator as mild in severity and not related to the study drug. The event occurred on Day 494, lasted 145 days, no action was taken with the study drug, and the event was considered resolved on Day 638.

CHMP comments:

The TEAE suicidality is not considered related to treatment by the investigator and is already stated in the SmPC of Fycompa.

- **Other safety findings**

- Laboratory results

There were no clinically important changes in mean hematology, chemistry, or urinalysis values from baseline to end of data cut-off for subjects in Extension B.

There were some markedly abnormal laboratory values: markedly abnormal hematology values were observed in 4 subjects in the POS cohort (3 [8.1%] subjects with markedly abnormal low neutrophil counts and 1 [2.7%] subject with markedly abnormal low hemoglobin).

One subject in the POS cohort had a markedly abnormal clinical chemistry results of high GGT.

There were no markedly abnormal urinalysis values.

CHMP comments:

No clinical concerns were identified based on analysis of markedly abnormal laboratory results. The abnormal clinical laboratory values were sporadic and there were no consistent trend suggestive of clinical concern.

- Vital signs

No changes of clinical importance in mean vital signs values over time and no shifts of clinical concern in vital signs values were observed. There was a mean (SD) increase in body weight of 6.20 (3.675) kg from baseline to end of treatment. This magnitude of change is expected for growing children up to 12 years of age and thus of no clinical concern. No meaningful difference in vital sign results across age or concomitant EIAEDs cohorts were observed.

Clinically notable low vital sign results were reported and included systolic blood pressure (5 [12.8%] subjects) (criteria: <90 mmHg and decrease of ≥20 mmHg); diastolic blood pressure (4 [10.3%] subjects) (criteria: <50 mmHg and decrease of ≥15 mmHg); and pulse rate (1 [2.6%] subject) (criteria: <50 bpm and decrease of ≥15 bpm).

Clinically notable high vital sign results were reported and included pulse rate (1 [2.6%] subject) (criteria: >120 bpm and increase of ≥15 bpm) and weight (37 [94.9%] subjects) (criteria: increase of >7%).

CHMP comments:

No clinical concerns were identified based on analysis of these clinically notable results. The abnormal low or high vital signs values were sporadic and there were no consistent trend suggestive of clinical concern.

- Electrocardiograms

Not recorded.

Rapporteur's overall Conclusion on safety data of Extension B

The results from the data collected in Extension B in children aged 4 to <12 years of age receiving adjunctive perampanel therapy showed that:

- The incidence of TEAEs was similar across the cohorts of disease, age, and concomitant EIAEDs use. Most frequently reported TEAEs that occurred in more than 10% of subjects overall were nasopharyngitis, influenza, pneumonia, and vomiting.

- The majority of SAEs and other significant events of interest were transient and manageable meaning that subjects recovered without sequelae.

- There were no trends of clinical concern identified based on analysis of markedly abnormal laboratory results and shifts of laboratory parameters over time as well as no trends of clinical concern based on analysis of vital signs, including body weight (normal weight gain for growing paediatrics, only one subject with a weight gain of > 7%).

- Long-term daily doses of perampanel oral suspension (overall median duration of exposure of 116.7 weeks i.e. > 2 years) were generally well-tolerated when administered as adjunctive therapy in children aged 4 to <12 years of age.

2.3.3. Discussion on clinical aspects

The Sponsor has submitted final study results and report related to paediatric population for Study E2007-G000-311 (referred to as Study 311). Study 311 was a Phase 3, multicentre, open-label, single-arm study in children (aged 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTCS). The study enrolled 180 subjects (planned 160 subjects) and all subjects were treated with perampanel in the study. Of note, 146 subjects completed the Core Study, of which 136 subjects entered Extension A. Fifty-three subjects completed Extension A in Japan or France (those eligible to enrol in Extension B), of which 43 subjects entered Extension B.

The primary objective of the study was to evaluate the safety and tolerability of perampanel oral suspension as an adjunctive therapy in children (aged 4 to <12 years) with inadequately controlled POS or PGTCS.

The Core and Extension A data were already submitted and assessed in a Type II variation, procedure EMEA\H\C\002434\II\0047, to extend the approved indication for Fycompa to paediatric POS patients 4 to less than 12 years and PGTC of IGE patients 7 to less than 12 years that was approved on 10 Nov 2020. The Extension B data were now available and assessed in this submission.

Regarding efficacy data, no data on the maintenance of efficacy were submitted and assessed within the scope of this report.

Regarding safety data, the results of Extension B of Study 311 show that Fycompa is overall well-tolerated as adjunctive treatment of epilepsy.

There were 35 (83.3%) subjects experienced TEAEs during this study (10 (90.9%) subjects in the 4 to <7 years cohort and 25 (80.6%) subjects in the ≥7 to <12 years cohort). The majority of TEAEs reported were deemed not related to perampanel. Treatment-related TEAEs were reported for 6 (14.3%) subjects overall. Of the 6 subjects, 1 (9.1%) subject was in the 4 to <7 years age cohort and 5 (16.1%) subjects were in ≥7 to <12 years age cohort. The treatment-related TEAEs included 1 yellow skin in a subject of the 4 to <7 years age cohort and 1 dysphagia, 1 DILI, 1 GGT increased, 1 headache and 1 somnolence in one subject each of the ≥7 to <12 years age cohort.

The majority of subjects experienced TEAEs that were either mild (14 [33.3%] subjects) or moderate (15 [35.7%] subjects) in severity. Overall, 6 (14.3%) subjects had severe TEAEs. Most severe TEAE were related to infections and infestations or respiratory, thoracic and mediastina disorders MedDRA SOC.

There were 8 (19.0%) subjects who reported SAEs during Extension B of the study. None of the 8 SAEs (enterocolitis, bronchitis, lower respiratory tract infection, pharyngitis, pneumonia, pyelonephritis acute, pneumonia aspiration, upper respiratory tract inflammation, subgaleal haematoma) was assessed by the investigator as related to study drug. All occurred in the POS cohort and none in the PGTCS cohort.

No TEAEs leading to death, life-threatening situations, persistent or significant disability or incapacity or important medical events were reported during Extension B of the study.

No subject in Extension B discontinued the study drug due to a TEAE. Overall, TEAEs leading to dose reduction were reported by 2 (4.8%) subjects (both in the SGTCS subset of the POS cohort). Both subjects were in the ≥7 to <12 years and without-concomitant-EIAEDs cohorts. There were no subjects with TEAEs that led to dose interruption, dose increase or withdrawal

The AEs described in Extension B of Study 311 are consistent with the known safety profile for Fycompa described in the SmPC and do overall not differ between both age cohorts (4 to <7 years cohort and ≥7 to <12 years cohort). A review of these AEs does not suggest novel or unexpected safety signals emerging during the Extension B of the study. There were no significant changes in the frequency and severity of previously identified adverse reactions or important/potential risks.

On the basis of a review of the TEAEs in Extension B of Study 311, no additional changes to the SmPC safety information are considered necessary at this time. The data submitted do not influence the benefit-risk balance for Fycompa. Fycompa continues to show a favorable benefit-risk profile for the treatment of indicated seizure types.

3. CHMP overall conclusion and recommendation

Extension B of Study 311 did not change the benefit risk profile of perampanel as adjunctive treatment of focal seizures with or without SGS in patients from 4 years of age and older and of primary generalised tonic-clonic seizures in patients from 7 years of age and older with idiopathic generalised epilepsy.

The submission of this paediatric study pursuant to article 46 of Regulation (EC) No 1901/2006 did not provide new relevant clinical information on the safety in the targeted paediatric population.

No additional changes to the Summary of Product Characteristics (SmPC) are requested which is endorsed. The submitted data do not put into question the well-known benefit to risk balance for perampanel for the adjunctive treatment of:

- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.

- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

☒ Fulfilled: